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TITLE: Topical Rapamycin Therapy to Alleviate Cutaneous Manifestations of Tuberous Sclerosis Complex

PRINCIPAL INVESTIGATOR: Mary Kay Koenig, MD

CONTRACTING ORGANIZATION: University of Texas Medical School at Houston
Houston, TX 77030

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Mary Kay Koenig, MD
E-Mail: mary.k.koenig@uth.tmc.edu

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14. ABSTRACT Tuberous Sclerosis Complex (TSC) is a genetic disorder resulting from mutations in either the TSC1 or TSC2 genes. TSC is characterized by abnormal skin pigmentation and tumor formation in multiple organ systems. The *TSC1* and *TSC2* gene products are involved in cell signaling; in particular they are involved in the mammalian target of rapamycin (mTOR) signaling pathway. In TSC, the epidermal basal cells contain a mutant copy of either the *TSC1* or *TSC2* gene. A loss of heterozygosity results in constitutive activation of mTOR leading to production of epidermal cells at a faster rate than the ability to slough the dead cells. This overproduction of skin cells, in conjunction with angiogenesis, results in the formation of visible facial angiofibromas over time.
The lesions appear as red or pink papules distributed over the central face, especially on the nasolabial folds, cheeks, and chin. Lesions appear in early childhood and are present in up to 80% of TSC patients. Facial angiofibromas create considerable cosmetic morbidity for patients with TSC and currently there is no effective method for preventing or permanently removing them. Rapamycin is a naturally occurring antifungal macrolide that binds with high specificity to mTOR resulting in inhibition of mTOR activity and ultimately in downregulation of cell growth. Systemically administered rapamycin has an unfavorable side effect profile, limiting its potential use. Commonly reported side effects include oral ulcers, hyperlipidemia, thrombocytopenia, acneiform rash, immunosuppression, and impaired wound healing. Rapamycin has a molecular weight of 914.2 grams, allowing for its absorption through the superficial layers of the epidermis. With an appropriate delivery system, topically applied rapamycin should be able to penetrate the skin and reach the deep epidermal basal cells implicated in development of facial angiofibromas without causing side effects seen with systemic administration. This project is a multi-center prospective, randomized, double-blind, placebo-controlled evaluation of the safety and efficacy of a topically applied formulation of rapamycin to cutaneous angiofibromas in subjects with TSC. The primary goal is to evaluate the efficacy of the topical medication to reduce the appearance of cutaneous angiofibromas in patients with TSC. The secondary goal of this study is to confirm the safety of the topical medication. During the 1st year of the project, pre-clinical evaluations have occurred to ensure the purity, bioavailability, stability, and lack of cumulative irritation of the investigational product. The research protocol has been reviewed by independent review boards at each site where study subjects are being enrolled and individual study sites are being trained on trial procedures and protocols. During the 1st, 2nd and 3rd years of the project, 230 subjects will be enrolled into the study. Following enrollment, study subjects will apply either a skin coating containing rapamycin or a skin coating alone nightly to their angiofibromas. Each subject will use the investigational product for a total of 6 months. Photodocumentation will occur monthly and rapamycin blood levels will be drawn monthly to confirm lack of absorption.Following completion of the study, photographs will be evaluated by an independent dermatologist blinded to both the treatment arm and the stage of treatment. The dermatologist will assess each photograph's appearance using the facial angiofibroma grading scale and will compare photographs taken at study visit #1 (prior to treatment) and at study visit # 7 (upon completion of treatment).

15. SUBJECT TERMS
Tuberous Sclerosis Complex, Rapamycin, Angiofibroma, Sebaceous Adenoma

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INTRODUCTION

Tuberous Sclerosis Complex (TSC) is a genetic disorder characterized by abnormal skin pigmentation and tumor formation in multiple organ systems. TSC affects 1 in 7000 individuals worldwide. Common symptoms of TSC include: learning disabilities, mental retardation, seizures, skin lesions, kidney tumors, lung disease, heart tumors, and brain tumors. Facial angiofibromas are benign skin tumors found on the faces of patients with TSC. The angiofibromatous lesions appear as red or pink papules distributed over the central face, most notably on the nasolabial folds, cheeks, and chin. Lesions appear in early childhood and are present in up to 80% of TSC patients. These facial lesions create considerable cosmetic morbidity for patients with TSC. Since the initial descriptions of facial angiofibromas in the 19th Century, multiple treatments have been developed attempting to alleviate the appearance of these lesions. Treatments have included curettage, cryosurgery, chemical peels, dermabrasian, shave excisions, and laser therapy. Although the majority of these treatments are initially effective, they are uncomfortable and over time the lesions recur. Currently there is no effective method for preventing or permanently removing facial angiofibromas in patients with TSC. This study is designed to see if an investigational topical product applied to the face in people with tuberous sclerosis complex can decrease the appearance of facial angiofibromas. 230 study subjects will apply either a placebo or the investigational product nightly to their lesions for six months. The goal of this study is to develop a form of rapamycin that will provide a safe, effective treatment for facial angiofibromas in patients with tuberous sclerosis complex.

REPORT

Specific Aim 1: Obtain appropriate regulatory approvals and complete the preclinical evaluation of the topical product.

- Under the PI's supervision, Doyle's Pharmacy is responsible for the formulation, chemistry, manufacturing and control of the drug product.
  1. The study drug and controls have been successfully formulated and optimized with rapamycin concentrations of placebo (0.00%), low dose (0.10%), and high dose (1.0%).

2. Testing has shown stability for at least 90 days of the drug formulation. Doyle's Pharmacy continues to monitor drug stability to determine the maximum length of stability of the newly formulated drug product.
3. Doyle's Pharmacy is manufacturing the study drug adhering to FDA Good Manufacturing Practices for distribution to study subjects via individual study sites.

Specific Aims 2 and 3: Determine if the application of the topical rapamycin to the skin reduces the appearance of facial angiofibromas in TSC. Confirm the lack of systemic uptake of topically applied rapamycin and monitor for adverse events.

- The research protocol has been approved by the University of Texas at Houston (primary site) Internal Review Board (IRB) and the Department of Defense Human Research Protection Office (HRPO).
- The protocol has been approved by the following collaborating site's local IRBs: Minnesota, University of Alabama at Birmingham, and Sydney, Australia.
- The protocol has been approved by the HRPO for the following collaborating sites: Minnesota, University of Alabama at Birmingham, and Sydney, Australia.
- Site initiation visits and photography training have been completed for: UT Houston, Minnesota, University of Alabama at Birmingham, and Sydney, Australia.
- The following sites are currently enrolling study subjects: UT Houston, Minnesota, and Sydney, Australia.
- Trial monitoring is done throughout the study and site visits will be performed as sites arrive at the midpoint of the study for their site.
- Safety monitoring is done monthly with review of lab results and case report forms by Patti Tate and Drs. Joshua Samuels.
- Adverse Events and Serious Adverse Events are reviewed by Patti Tate, Dr. Joshua Samuels and Dr. Gretchen Von Allmen. The DSMB will meet when 50 subjects have been enrolled to review the case report forms and lab results.
- Data analysis will be done when all sites have completed enrollment and all study visits.

- Dissemination/Sharing of Results will be completed with publication of a manuscript when all the sites have completed the study and data has been analyzed.

KEY RESEARCH ACCOMPLISHMENTS

- The study drug has been successfully formulated and stability proven. It has been successfully manufactured in large batches for site distribution.
- Research protocols have been approved through local IRB and HRPO for 4 of the 11 clinical sites. Additional sites have protocols submitted to local IRBs and approval is pending.
- Photography training has been completed and site initiation visits performed for 4 of the 11 clinical sites.
- 4 of 11 clinical sites have begun enrolling study subjects.

REPORTABLE OUTCOMES

- As of the date of report, no subject has completed the trial and no data has been analyzed so no outcomes are available to report.
- Safety data is scheduled for review by the DSMB following enrollment of 50 subjects. This should occur prior to the end of the calendar year 2012. Following initial safety review, any reportable outcomes will be assessed.

CONCLUSION

- UT Houston, Minnesota, and Sydney, Australia have begun subject enrollment. Study subjects and investigators have noticed a subjective improvement in some study subjects, but as data has yet to be analyzed, no conclusive evidence of efficacy has been drawn. There have been no serious adverse events and no changes to the protocol are anticipated. Completion of the study, including the publication of results, is excepted by the summer of 2014.

REFERENCES

- No new publications/references are available relevant to the current study.

APPENDICES

- None.

SUPPORTING DATA

- None.